Emerging Patterns and Current Trends of AIDS Defining and Non-AIDS Defining Malignancies in HIV Infected Individuals from a Tertiary Care Center in South India

Cheryl Sarah Philipose (✉ cherylphilipose@yahoo.com)

Kasturba Medical College

Sruthi Sundar

Kasturba Medical College

John T Ramapuram

Kasturba Medical College

Sharada Rai

Kasturba Medical College

Ria Mukerjee

Kasturba Medical College

Research Article

Keywords: HIV, AIDS defining malignancies, non-AIDS defining malignancies.

Posted Date: July 9th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-665698/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background: People living with HIV/AIDS are at increased risk of developing malignancies- both AIDS defining and non-AIDS defining. The trends in incidence and severity of cancers among those with HIV/AIDS has greatly changed since the advent of ART. The aim of this study was to analyse the clinico-epidemiological profile of patients in South India with HIV/AIDS who subsequently developed malignancy.

Methods: A retrospective study was conducted by reviewing the medical records of patients with HIV/AIDS who were diagnosed with cancer after seroconversion from January 2014 to December 2019 and presented to a tertiary medical centre.

Results: Of the 627 cases of HIV presenting to the hospital during the study period, 50 (8%) developed cancer. Among the patients with cancer 14 (28%) had AIDS defining cancer while 36 (72%) had non- AIDS defining cancer. The mean CD4 cell count at the time of diagnosis with malignancy was 502.45/uL.

Among the patients with AIDS defining malignancies, 10 patients (71.4%) had NHL, 3 patients (21.4%) had invasive cervical cancer and one patient (7.1%) was diagnosed with CNS lymphoma. Among the 36 cases of non-AIDS defining malignancies, there were 7 cases (19.4%) of malignancies of the upper airway (oral cavity, nasopharynx, larynx), 7 cases (19.4%) of malignancies of the female genital tract, 6 cases (16.7%) of haemato-lymphoid malignancies, 3 cases each (8.3%) of malignancies of the lung and GIT including anal canal. 2 cases each (5.6%) of breast carcinoma or carcinoma of the male genital tract. 1 case each (2.8%) of cancers of the eye, urinary tract and metastatic lesion with an unknown primary were also reported.

Conclusion: Malignancies in HIV infected individuals in an emerging global health issue. In the present study, we report a prevalence of 8% of malignancies in HIV infected individuals and a higher incidence of non-AIDS defining malignancies.

Introduction

HIV is a major global pandemic with high morbidity and mortality. The World Health Organisation (WHO) estimates that around 38 million people are presently living with HIV, which include breastfeeding mothers and children. Worldwide, there have been around 6,90,000 deaths attributable to HIV. ^{1,2} In India, although current trends show a decline, there is still a significant 23.48 lakh population living with HIV and 69.22 thousand newly diagnosed cases every day.³

The development of Anti-Retroviral Therapy (ART) substantially reduced mortality rates in HIV infected individuals. ⁴ However, this increased longevity had nonetheless led to other challenges, namely, development of other complications including malignancies, opportunistic infections and cardiovascular diseases in this cohort of patients, that may be attributable to either ART or due to HIV infection itself. ⁵ Traditionally, malignancies in HIV infected individuals have been classified into AIDS-defining (Non-

Hodgkin lymphoma, Kaposi sarcoma, cervical carcinoma) and non-AIDS defining malignancies.²² It is increasingly observed that there is a changing trend with development of non-AIDS defining malignancies in the HIV-infected individuals who are receiving ART therapy, as compared to the AIDS-defining malignancies such as Kaposi's sarcoma and Non-Hodgkin lymphoma (NHL) that were traditionally reported in the pre-ART era. It has been reported that HIV infected individuals are at an increased risk for Non-AIDS defining malignancies such as Hodgkin lymphoma (HL), anal carcinomas and lung carcinomas. Few studies have described the survival outcomes of HIV infected individuals with malignancies and have observed a poorer outcome in them.⁶

Although the rates of opportunistic infections have declined with introduction of ART, they still remain an important cause of mortality in HIV infected individuals, particularly due to late detection as well as lower CD4 cells counts.. These include *Pneumocystis jiroveci*, toxoplasma, candida, tuberculosis and cryptococcus.^{7,8} Some of the opportunistic infections have oncogenic potentials and are implicated in the development of various malignancies including Kaposi Sarcoma Virus, Epstein Barr virus (EBV) and Human Papilloma Virus (HPV) leading to Kaposi's sarcoma, non-Hodgkin lymphoma, cervical and anal carcinomas respectively.⁹

Estimation of CD4 cell count reflects the immune status of the individual, and is used in the management and prognosis of HIV. With the natural progression of disease, there is a decline in CD4 cell counts that heightens the risk for malignancies, cardiovascular disease and opportunistic infections. Moreover, a low CD4 cell count has also been seen to precede a diagnosis of Hodgkin lymphoma.¹⁰

Majority of studies on the prevalence of AIDS defining as well as non-AIDS defining malignancies are from Western Literature. There is paucity of literature of AIDS related cancers from India, despite being having one of largest global burden of HIV/AIDS. Knowledge about patterns and emerging trends of cancers in HIV patients may provide crucial insight into the pathobiology of HIV and may be of vital importance in prediction, risk stratification, screening, early detection and management of cancers in HIV infected individuals.^{11,12}

The aim of the present study is to study the emerging patterns and current trends of AIDS defining and non-AIDS defining malignancies in HIV infected individuals.

Materials And Methods

The present study is a retrospective study conducted in the Department of Pathology at Kasturba Medical College, Mangalore from January 2014 to December 2019. Institutional Ethics committee clearance was obtained prior to the commencement of the study. All cases of HIV infected individuals in the study period who were subsequently diagnosed with cancer following seroconversion were included in the present study. The patients without a documented HIV positive test, those with cancer prior to HIV seroconversion and patients without histopathological confirmation of malignancy were excluded from the present study. In selected cases, the demographic data, clinical history, examination findings and treatment details,

relevant laboratory investigations including HIV viral loads, CD4 lymphocyte counts, serum tumour markers, cytology reports, radiological investigations and histopathology reports were recorded from the patients' case files. The results thus obtained was tabulated and analyzed. Statistical analysis was performed by SPSS software, version 18.

Results

The present study included 627 HIV patients who visited the hospital during the study period. The age of the patients ranged from 1 to 75 years with a mean age of 42.9 years. Of the 627 patients, 382 patients were male (n = 627, 60.9%) and 245 patients were women (n = 627, 39.1%).

The most common cause for hospitalization among HIV infected patients was pulmonary tuberculosis (n = 86, 13.7%), followed by pneumonia (n = 71, 11.3%), and extra-pulmonary tuberculosis (n = 58, 9.3%). Of the cases of extrapulmonary tuberculosis (n = 58) there were 33 cases of tubercular meningitis/tuberculoma (58.9%, n = 58), 10 cases of abdominal tuberculosis which accounted for 17.5% of extrapulmonary tuberculosis cases, 13 cases (22.4%) of tubercular lymphadenitis and 1 case (1.7%) each of tubercular pericarditis and spinal tuberculosis (Pott's disease). There were 32 cases of disseminated tuberculosis (5.1%).

50 HIV infected patients were diagnosed with malignancy after diagnosis of HIV.

The overall prevalence of malignancy was 8% (n = 50).

ART therapy:

Of the total patients, 403 patients were on ART (64.3%), with 356 patients (56.8%) on first line ART and 47 patients (7.5%) on second line ART. Of the 356 patients on 1st line ART, 24 patients (6.7%) subsequently developed cancer whereas among the 47 patients on second line ART, 3 (6.3%) developed cancer. 121 patients (19.3%) patients who visited the hospital did not receive ART. Of these patients 21 (17.35%) went on to develop cancer. 10 (1.6%) patients discontinued treatment after initiating ART; among them 2 patients (20%) went on to develop cancer.

The demographic data of the HIV patients with malignancy is depicted in Tables 1 and 2.

Table 1
AIDS defining cancers:

Sl No	Age	Sex	Presenting complaints	Final diagnosis
1	47	Male	Headache since 7 days	CNS lymphoma
2	59	Male	Fever, myalgia and cough with expectoration since 2 days, previous history of Non Hodgkins Lymphoma 6 years ago	Non Hodgkin's Lymphoma
3	7	Female	Abdominal distension and weight loss since 1 month	Diffuse large B cell lymphoma of stomach
4	67	Female	Weakness and altered sensorium since 1 week	Stage 4 diffuse large B cell lymphoma
5	52	Female	Swelling in the left side of the neck since 20 days	Non Hodgkins lymphoma- B cell lymphoblastic lymphoma
6	37	Male	Fatigue, malaise and tiredness since 1 month. Past history of Non Hodgkin's lymphoma.	Relapse of Non Hodgkin's Lymphoma
7	44	Male	Weight loss and anorexia since 1 month	Non Hodgkins Lymphoma- Diffuse large B cell lymphoma of the appendix, ileocaecal region and terminal ileum.
8	48	Male	Significant weight loss since 1 year. Epigastric pain since 1 month. Altered bowel habits: constipation, nausea, vomiting since 4 days.	Non Hodgkin's lymphoma of the jejunum
9	55	Male	Swelling in the neck since the last 2 months	Non Hodgkins Lymphoma of cervical lymph node
10	38	Male	Swelling and throbbing pain over the same in the submandibular area since 1 month.	Non Hodgkin's lymphoma of the submandibular salivary gland
11	45	Male	Mass in the mouth since 1 month, generalized weakness since 25 days	Extramedullary plasmacytoma of plasmablastic type of the upper right buccal vestibule
12	55	Female	Postmenopausal bleeding and lower pain abdomen since 6 months	Poorly differentiated squamous cell carcinoma of the cervix
13	35	Female	Irregular menstrual cycles since last 1 month	Moderately differentiated squamous cell carcinoma of the cervix

Sl No	Age	Sex	Presenting complaints	Final diagnosis
14	43	Female	Recurrent oral ulcers since 1 year, tingling sensation over right thigh since 1 month; Per speculum examination revealed erosions over both lips of the cervix and bleeding from the os	Squamous cell carcinoma of the cervix

Table 2
Non AIDS defining cancers:

Sl No	Age	Sex	Presenting complaint	Final diagnosis
1	54	Male	Multiple swellings over left side of neck since 3 years	EGFR positive adenocarcinoma of lung
2	56	Male	Cough with expectoration and breathlessness since 2 months. Chronic smoker for the last 30 years	Squamous cell carcinoma of lung with malignant pericardial effusion.
3	58	Male	Known case of RVD and lung cancer, referred from another centre post chemoradiation with severe pain over right side of chest since 1 day	Squamous cell carcinoma of lung
4	47	Female	Pt was referred from another center after having been diagnosed with maxillary carcinoma	Sinonasal carcinoma
5	45	Male	Pain and swelling in left side of tongue since 20 days	Well differentiated squamous cell carcinoma of the tongue
6	58	Female	Swelling in the R side of the oral cavity for 4 months- associated with continuous pain which is present over the swelling and referred to the R ear and temporal region.	Well differentiated squamous cell carcinoma of the right lower alveolus
7	66	Female	Pain and visible ulcer over the right side of the tongue	Well differentiated squamous cell carcinoma of the tongue
8	62	Female	Progressively increasing swelling and pain over the left lower jaw and trismus since 6 months.	Moderately differentiated squamous cell carcinoma of the lower lip.
9	48	Female	Dysphagia and weight loss since 1 month	Moderately differentiated squamous cell carcinoma of mouth.
10	54	Male	Bleeding from nose, nose block and anosmia since 1 week	Paranasal (maxillary and ethmoidal) sinus malignancy
11	49	Male	Swelling over the right side of perineum since 2 years, pain over the swelling since 1 year	Well differentiated squamous cell carcinoma of the anal canal

Sl No	Age	Sex	Presenting complaint	Final diagnosis
12	47	Male	Pain and swelling in the perineal area since 2 months	Squamous cell carcinoma of the anal canal
13	43	Male	Painful swelling over the perineum since 2 months. Lower back pain since 2 months.	Poorly differentiated squamous cell carcinoma of the anal canal
14	67	Male	Generalized weakness since 1 month. Dysphagia since 10 days- more for solids than liquids. Loss of weight and appetite.	Oesophageal adenocarcinoma
15	40	Male	Intermittent episodes of pain abdomen since 4 months. Significant weight loss. Diagnosed to have cystic pancreatic neoplasm at another centre and referred for treatment.	Cystic neoplasm of pancreas
16	49	Female	Generalized weakness and fatigue since 1 month.	Large space occupying lesion of the liver- maybe hepatocellular carcinoma
17	61	Male	Known case of metastatic renal cell carcinoma- came with complaints of weakness of left side of body after 7 cycles of chemotherapy	Metastatic renal cell carcinoma
18	48	Male	Painful bleeding ulcer over shaft of penis with enlarged R inguinal lymph nodes	Well differentiated squamous cell carcinoma of the penis
19	48	Male	Known case of penile cancer with partial penectomy done previously- came with cough with expectoration since 1 month	Moderately differentiated squamous cell carcinoma of the penis
20	36	Female	Routine PAP smear showed evidence of atypical cells	Cervical carcinoma in situ
21	42	Female	Routine USG showed hypoechoic lesion in anterior wall of cervix	Endometrial stromal neoplasm
22	36	Female	Routine PAP smear showed atypical cells	Cervical carcinoma in situ
23	50	Female	Bilateral lower limb swelling since 8 months, Abdominal distention since 5 months, breathlessness since 1 month	Serous cystadenoma of the ovary
24	55	Female	Known case of ovarian cancer who underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy and came for chemotherapy	Ovarian malignancy

Sl No	Age	Sex	Presenting complaint	Final diagnosis
25	46	Female	Routine abdominal ultrasound showed the presence of a lesion in the anterior wall of the cervix; so pt came for a fractional curettage and cervical biopsy	Endometrial stromal neoplasm
26	34	Female	Fever and headache since 16 days	Cervical carcinoma in situ
27	36	Female	Patient came for follow up from another hospital after having done a bilateral mastectomy for breast cancer	Carcinoma Left breast
28	39	Female	Patient came after having undergone a modified radical mastectomy for initiation of chemotherapy	Infiltrating ductal carcinoma
29	55	Male	Persistent fever, lymphadenopathy and reduced appetite since 10 days, Low back ache and bilateral lower limb pain since 20 days	Acute leukaemia
30	50	Female	Low back ache since 3–6 months	Multiple myeloma IgG lambda
31	36	Male	Bilateral neck swellings since 6 months	Hodgkin's lymphoma-mixed cellularity subtype
32	46	Male	Bilateral neck swelling since 6 months	Hodgkin's lymphoma
33	49	Male	Pain bilaterally present in both upper and lower limbs, nausea and loss of appetite since 3 days	Multiple myeloma
34	63	Male	Severe hip pain radiating to the lower leg	Multiple myeloma IgG kappa
35	56	Male	Bilateral inguinal swelling since 1 year	Squamous cell carcinoma with occult primary
36	47	Female	Whitish lesion over R eye since 6 months	OSSN- Ocular surface squamous neoplasm-invasive squamous cell carcinoma

There were 50 HIV patients who had cancer. The mean age of HIV patients who developed cancer was 48.16 years (Age range: 7–60 years). Of these, 27 were male (54%) and 23 were female (46%).

7 patients (14%, n = 50) presented with complaints of a swelling in the neck. 5 patients (10%, n = 50) presented to the hospital with pain and a swelling or ulcero-proliferative growth. 10 patients (20%, n = 50) were referred from other centers.

CD4 cell count:

Of the 50 patients who developed malignancy, details of the CD4 cell count at the time of initial diagnosis with HIV were available in 16 patients. The mean CD4 cell count at the time of diagnosis of HIV was 407.31/uL. Among them 3 patients (18.8%, n = 16) had a CD4 cell count < 50 at the time of diagnosis, 3 (18.8%) had a CD4 cell count of 150–200/uL and 3 (18.8%, n = 16) had a CD4 cell count > 1000/uL at the time of diagnosis.

Details of the CD4 cell count at time of diagnosis of malignancy was available in 29 patients. The mean CD4 cell count at the time of diagnosis with malignancy was 502.45/uL. Among these, 4 patients (13.8%, n = 29) had a CD4 cell count of < 50/UI and 3 patients (10.3%, n = 29) had a CD4 count of 400–450/uL.

28 patients (56%) were diagnosed with malignancy within the first 5 years of being diagnosed with HIV. 16 patients (32%, n = 50) were diagnosed with cancer within 5–10 years of being diagnosed with HIV.

27 (54%) were on treatment with first line ART and 3 (6%) were on second line ART. 13 patients (26%) were not on treatment while 3(6%) discontinued treatment. The data of ART treatment was unavailable for 4 patients.

14 patients (28%) had AIDS defining malignancies while 36 patients (72%) had non-AIDS defining malignancies.

HIV & malignancies

There were 14 cases with AIDS defining malignancies and 36 cases with non-AIDS defining malignancies.

Treatment modalities:

The most common treatment modality for those patients with cancer and HIV was chemotherapy which was received by 13 patients (26%), followed by surgery which was performed for 9 patients (18%), and concurrent chemo-radiation in 7 patients (14%).

Follow up data:

Follow up data was available for 24 patients. On follow, 7 patients (14%, n = 50) recovered after treatment, 5 patients (10%) developed complications linked to chemo-radiation and 6 (12%) patients developed other complications which were unrelated to treatment. 4 patients (8%) refused treatment and 2 patients (4%) succumbed to their illness. 26 patients (52%) were lost to follow up.

Opportunistic infections:

The most common opportunistic infection among patients with HIV and malignancy was pulmonary tuberculosis (n = 3,6%). 3 patients were diagnosed with CNS tuberculoma, herpetic skin lesions and Pneumocystis jiroveci pneumonia respectively (4%).

AIDS defining malignancies:

The mean age of patients with AIDS defining malignancies was 45.14 years (Age range: 7–67 years). Of these patients, 8 (57.1%) were male and 6 (42.9%) were female. 9 patients (64.3%) were diagnosed with a malignancy within the first 5 years of being diagnosed with HIV. Among the patients with AIDS defining malignancies, 10 patients (71.4%) had NHL, 3 patients (21.4%) had invasive cervical cancer and one patient (7.1%) was diagnosed with CNS lymphoma. There were no cases of Kaposi's sarcoma in the present series.

3 cases diagnosed with invasive cervical cancer were associated with HPV (21.4%). Two patients (14.28%, n = 14) presented with metastasis.

Non-AIDS defining malignancies:

Among the 36 cases of non-AIDS defining malignancies, the mean age at the time of diagnosis was 49.33 years (range 34–67 years). Of these, 19 patients (52.8%) were male while 17 (47.2%) were female.

20 patients (55.6%) were on treatment with first line ART and 10 patients (27.8%) were not on any treatment.

19 patients (52.8%) were diagnosed with a non-AIDS defining cancer within the first 5 years of being diagnosed with HIV and 14 patients (38.9%, n = 36) were diagnosed with a non-AIDS defining cancer within 5–10 years of being diagnosed with HIV.

Among the 36 cases of non-AIDS defining malignancies, there were 7 cases (19.4%) of malignancies of the upper airway (oral cavity, nasopharynx, larynx), 7 cases (19.4%) of malignancies of the female genital tract, 6 cases (16.7%) of haemato-lymphoid malignancies, 3 cases each (8.3%) of malignancies of the lung and GIT including anal canal. 2 cases each (5.6%) of breast carcinoma or carcinoma of the male genital tract. 1 case each (2.8%) of cancers of the eye, urinary tract and metastatic lesion with an unknown primary were also reported.

Among the 3 cases of lung carcinomas, 2 (66.7%) were cases of squamous cell carcinoma of lung and 1 (33.3%) was a case of adenocarcinoma of lung.

Among the 7 cases of malignancy of the upper airway (oral cavity, nasopharynx and larynx) there were 3 cases (42.9%) of carcinoma of the tongue, 2 cases (28.6%) of paranasal sinus malignancy, 1 case each (14.3%) of carcinoma of the buccal mucosa and the alveolus/ jaw.

There were 3 cases of squamous cell carcinoma of the anal canal and 3 cases of carcinomas of the GIT excluding the anus; among these, there was 1 case each (33.3%) of oesophageal adenocarcinoma, pancreatic cystic neoplasm and hepatocellular carcinoma.

There was 1 case of metastatic renal cell carcinoma.

There were 2 cases of squamous cell carcinoma of the penis.

There were 7 cases of carcinomas of the female genital tract, of which 3 (42.9%) were cases of non-invasive cervical carcinoma, 2 cases (28.6%) of ovarian carcinoma and 2 cases (28.6%) of endometrial stromal sarcoma.

Among the malignancies of the breast, there were 2 cases of infiltrating ductal carcinoma.

There were 6 cases of haemato-lymphoid malignancies. Among them, there were 3 cases (50%) of multiple myeloma, 2 cases (33.3%, n = 6) of Hodgkin lymphoma and 1 case (16.7%) of leukaemia.

There was 1 case of metastasis with an unknown primary and 1 case of an ocular surface squamous neoplasm.

HPV linked and non-HPV linked malignancies:

Among the malignancies, 16 patients (32%) had HPV linked malignancies, while 34 patients (68%) had non-HPV linked malignancies.

13 non AIDS defining malignancies (36.1%) were associated with HPV while 23 cancers did not show any association with HPV (63.9%).

The HPV linked cancers included 3 cases of invasive cervical cancer, 3 cases of squamous cell carcinoma of the anal canal, 3 cases of squamous cell carcinoma of the tongue, 2 cases of sinonasal carcinoma, 1 case each of squamous cell carcinoma of the buccal mucosa and the alveolus.

Treatment details & Follow up data:

The most commonly used treatment modality was chemotherapy that was received by 10 patients (27.8%).

6 patients (16.7%) recovered after treatment, 5 patients (13.9%) developed complications linked to chemo-radiation and 4 patients (11.1%) developed complications unrelated to therapy. The follow up records were not available for 17 patients.

6 patients (12%) had demonstrable evidence of distant metastasis at the time of diagnosis, while 44 patients (88%) did not have metastasis.

Young HIV patients with malignancy:

A 7-year old girl with diffuse large B cell lymphoma of the stomach was the only case of cancer among HIV infected children in the study. The child presented with abdominal distension and weight loss since one month, along with pedal oedema since 1 week. The child was not on ART. The CD4 count at the time of diagnosis with HIV was 283. Endoscopy guided biopsy revealed diffuse large B cell lymphoma of the stomach. CT scan showed metastasis. The patient party was counselled about the necessity of PET/CT and other investigations as well as potential treatment options. However, patient party wanted to undergo

further treatment in their hometown. Hence, the child was given nutritional supplementation and discharged.

There were no cases of any malignancies among young adults of age group 18–25 years.

Discussion

HIV infected individuals are at an increased risk of developing cancer.¹³ In the early 1980's, reports of a cluster of cases of *Pneumocystis jiroveci* and an unusually aggressive malignancy, Kaposi's sarcoma in homosexual men drew attention to the rising AIDS pandemic. It soon spread throughout the globe and soon worldwide, there were increasing reports of certain specific cancers namely Kaposi's sarcoma, aggressive lymphomas and cervical cancers, which have now been termed as AIDS defining cancers. The discovery of Kaposi Sarcoma Herpes viruses that was responsible for development of Kaposi's sarcoma, led to the understanding of the oncogenic potential of other viruses including the Epstein Barr virus and Human Papilloma viruses.⁹

The present study included 627 HIV infected patients which included 50 cases of patients with HIV and malignancy. The majority of the patients were male and the mean age was 42.9 years. In a study by Venkatesh et al, the authors studied 42 patients with HIV and malignancy, in which majority of the patients were male. The mean age of the patients in the study was 35 years. These findings were similar to the present study.¹¹

The prevalence of malignancies in patients with HIV in the present study was found to be 8%. In a study done in Guinea, Traore et al. studied 2598 patients with cancer which included 54 patients with HIV and found a high prevalence of HIV (2.1%). They estimated that 30–40% of HIV patients are at a risk of developing malignancies.

Of the 50 patients, details of the CD4 cell count at time of diagnosis of malignancy was available in 29 patients. The mean CD4 cell count at the time of diagnosis with malignancy was 502.45/uL. Among these, 4 patients (13.8%) had a CD4 cell count of < 50/uL and 3 patients (10.3%) had a CD4 cell count of 400–450/uL.

In a study by Monforte et al. the researchers reported that lower CD4 cell counts were associated with higher mortality. They found that doubling the CD4 count led to a reduction in mortality to approximately half. Even among patients who received ART, the latest CD4 cell count as well as the nadir CD4 cell counts were independent predictors of mortality in HIV patients with AIDS defining malignancies.¹⁴

Other researchers have also similarly described the association of lower CD4 cell counts with risk of malignancy particularly for infection related cancers including Hodgkin lymphoma, cervical carcinomas, hepatocellular carcinomas and anal carcinomas.¹⁵

In a study by Clifford et al. the authors followed 7304 HIV patient records from the Swiss HIV Cohort Study and Swiss cantonal cancer registries. They reported that the standardized incident ratio for Kaposi's sarcoma and Non-Hodgkin's lymphoma had an inverse association with CD4 cell counts. However, this association was not observed for other malignancies including cervical carcinomas, for cancers of the lip, mouth, pharynx, trachea, lung, bronchus and non-melanomatous skin cancer. They concluded that patients who were on ART had a lower risk of Kaposi's sarcoma as well as Non-Hodgkin lymphoma. However, the benefit of ART therapy did not reduced risk of development of Hodgkin's lymphoma and other non-AIDS defining malignancies.¹⁶

In the present series, majority of the patients (72%) had a non-AIDS defining malignancies similar to the finding by Traore et al²⁵. The cases in the present study included malignancies of the oral cavity, nasopharynx, larynx, female genital tract, haematolymphoid malignancies, lung, GIT including anal canal, breast carcinoma, male genital tract, eye, urinary tract and metastatic lesion with an unknown primary.

HIV infected individuals have a two to four times higher risk of head and neck carcinomas and double the risk of oral cavity and pharyngeal carcinomas as cancer compared to HIV un-infected individuals. This may be attributable to HPV with studies showing a prevalence of oncogenic HPV ranging from 12–26% among HIV infected individuals. Of the various subtypes, HPV 16 has been implicated in over 80% of malignancies of the oropharynx.²⁴

There were 3 cases each of anal carcinomas, cervical carcinomas, multiple myelomas, lung and GIT excluding the anus.

In a study done in Guinea, authors reported that breast cancer was the most common non-AIDS defining malignancy, while lung malignancy was more common in developed countries, in contrast to the present study, where we found a lower incidence of both these malignancies. In another study by Venkatesh et al, the researchers found Hodgkin's lymphoma to be the most frequent malignancy among the non-AIDS defining malignancies, followed by breast carcinomas⁽¹¹⁾.

The AIDS defining malignancies accounted for only a minority of cases in the present study (28%). Among these, the most common was NHL, followed by cervical cancers. These findings were similar to that reported by Venkatesh et al and Traore et al^(11,25).

There were no reported cases of Kaposi's sarcoma in the present study. This was similar to findings reported by Phatak et al. The authors noted that AIDS defining cancers including Non-Hodgkin lymphoma and cervical carcinomas, were seen in 54.35% cases whereas non-AIDS defining cancers were noted in 45.65% cases. The authors too did observe Kaposi's sarcoma in their study. This was in contrast to another study from Nigeria that have found increased risk of development of Kaposi's sarcoma but neither Non-Hodgkin lymphoma or cervical carcinomas among HIV infected patients. This highlights significant demographic differences with respect to malignancies among HIV infected individuals in different parts of the world.^{17,18}

Among the malignancies, 16 patients (32%) had HPV linked malignancies, while 34 patients (68%) had non-HPV linked malignancies. Studies have reported a high incidence and prevalence of association of HPV as well as precursor lesions in patients with HIV as compared to the general population. These includes ano-genital malignancies including cervical carcinomas and anal carcinomas. Authors have reported that the risk of anal carcinomas is higher in homosexual men and have recommended screening the at-risk population. Similarly, current guidelines for HIV infected women recommend cytology screening once in every six months for 2 consecutive negative cytology results and thereafter yearly. Researchers have recommended colposcopic examination with acetic acid for cervical carcinoma screening in resource strapped countries to reduce the incidence of these cancers⁽²⁶⁾.

The risk of HPV related malignancies at other sites including oropharynx, penis, vulva, vagina have also been predicted to be increased although at present, data is limited with regard to these.^{19,20}

Presently, cancer screening plays a crucial role in the routine management of patients living with HIV, which would include an assessment of individual risk, survival, risks and benefits of screening as well as its potential outcome. Although the successful intervention in the form of cancer screening in general population has proved beneficial, data on similar intervention in HIV infected individuals is lacking. Sigal et al. provided a conceptual framework of screening for cancer in patients with HIV. This included a Pap test for cervical carcinomas, anal cytology test for anal carcinomas, abdominal ultrasound and AFP estimation for hepatocellular carcinomas. In addition to these, other screening modalities including mammography for breast carcinoma, fecal occult blood testing and sigmoidoscopy for colonic carcinoma, PSA test for prostatic carcinoma, CT scans in heavy smokers for lung carcinoma have been recommended by other authors.²¹

There was 1 case of malignancies in a child and no cases of malignancies in young adults. Researchers have reported highest frequency of Kaposi's sarcoma, NHL and leiomyosarcoma in the young. However, the child in our study had Non Hodgkins Lymphoma.

Yet another study by Dhokotera et al. studied 1853 cases of adolescent and young patients of HIV with malignancies and found maximal cases of Kaposi sarcoma, cervical carcinoma, Hodgkins lymphoma and anogenital carcinomas other than cervix.

Researchers have documented higher incidence of malignancies caused by oncogenic viruses attributable to high risk behavior in sexually active adolescents and adults such as cervical carcinomas, anogenital carcinomas and hepatocellular carcinomas. There remains a higher risk in those individuals who have perinatally acquired HIV infection, attributable to various factors including longer duration of infection with HIV, immune dysregulation and co-infection with HBV, HCV or both. Thus it is recommended that this unique cohort of young patients must be diagnosed at the earliest and started on ART therapy and that access to HPV and HBV vaccination as well as individualized cancer screening facilities should be provided in their multidisciplinary services.^{22,23}

Conclusion

Malignancies in HIV infected individuals in an emerging global health issue, particularly in young patients. In the present study, we report a prevalence of 8% of malignancies in HIV infected individuals and a higher incidence of non-AIDS defining malignancies. A multidisciplinary approach for early detection, along with initiation of ART therapy, access to vaccination and cancer screening facilities is recommended for HIV infected individuals.

Abbreviations

HIV: Human Immunodeficiency Virus

AIDS: Acquired Immunodeficiency Syndrome

WHO: World Health Organisation

ART: Anti Retroviral Therapy

HPV: Human Papilloma Virus

HL: Hodgkin Lymphoma

NHL: Non Hodgkin Lymphoma

Declarations

Ethics approval and consent to participate

The following study has been approved by the Institutional Ethics Committee.

Consent for publication

Consent form available

Availability of data and materials

The dataset analyzed during the current study is available from the corresponding author on reasonable request.

Competing interests

None

Funding

None

Authors' contributions

Authors contributed to the manuscript in the following ways: study concept and design (CSP,SRS,RM); acquisition, analysis, and interpretation of the data (CSP,SRS,JTR,SR,RM); drafting the manuscript (CSP,SRS); critical revision of the manuscript for important intellectual content (all authors); statistical analysis (CSP,SRS); administrative, technical, or material support (all authors); and study supervision (all authors). All authors have read and approved the final manuscript.

Acknowledgements

None

References

1. Frank TD, Carter A, Jahagirdar D, Biehl MH, Douwes- Schultz D, Larson SL et al. Global, regional, and national incidence, prevalence, and mortality of HIV, 1980-2017, and forecasts to 2030, for 195 countries and territories: a systematic analysis for the Global Burden of Diseases, Injuries, and Risk Factors study 2017. *Lancet HIV* 2019; 6(12): e831-859.
2. World Health Organization. Fact Sheets: HIV/AIDS. [Online]. 2020 Nov 30 [cited 2021 May 28]; Available from: URL: <https://www.who.int/news-room/fact-sheets/detail/hiv-aids>
3. National AIDS Control Organisation. HIV Facts & Figures. [Online]. 2019 [cited 2021 May 28]; Available from: URL: <http://naco.gov.in/hiv-facts-figures>
4. Kasamba I, Baisley K, Manyanja BN, Maher D, Grosskurth H. The impact of antiretroviral treatment on mortality trends of HIV-positive adults in rural Uganda: a longitudinal population- based study, 1999– 2009. *Trop Med Intl Health* 2012 Aug; 17(8): e66-73.
5. Data Collection on Adverse Events of Anti-HIV Drugs (D: A: D) Study Group. HIV-induced immunodeficiency and mortality from AIDS-defining and non-AIDS-defining malignancies. *AIDS* 2008 Oct 18; 22(16): 2143.
6. AE, Shiels MS, Suneja G, Engels EA. Elevated cancer-specific mortality among HIV-infected patients in the United States. *J Clin Oncol* 2015 Jul 20;33(21):2376.
7. Prasitsuebsai W, Kariminia A, Puthanakit T, Lumbiganon P, Hansudewechakul R, Moy FS, Law M, Kumarasamy N, Razali K, Sirisanthana V, Sohn AH. Impact of antiretroviral therapy on opportunistic infections of HIV-infected children in the TREAT Asia pediatric HIV observational database. *Pediatr Infect Dis J* 2014 Jul;33(7):747.
8. Galisteu KJ, Cardoso LV, Furini AA, Schiesari Júnior A, Cesarino CB, Franco C, Baptista AR, Machado RL. Opportunistic infections among individuals with HIV-1/AIDS in the highly active antiretroviral therapy era at a Quaternary Level Care Teaching Hospital. *Rev Soc Bras Med Trop* 2015 Apr;48(2):149-56.

9. Yarchoan R, Uldrick TS. HIV-associated cancers and related diseases. *N Eng J Med* 2018 Mar 15;378(11):1029-41.
10. Helleberg M, Kronborg G, Larsen CS, Pedersen G, Pedersen C, Obel N, Gerstoft J. CD4 decline is associated with increased risk of cardiovascular disease, cancer, and death in virally suppressed patients with HIV. *Clin Infect Dis* 2013 Jul 15;57(2):314-21.
11. Venkatesh KK, Saghayam S, Devaleenal B, Poongulali S, Flanigan TP, Mayer KH, Kumarasamy N. Spectrum of malignancies among HIV-infected patients in South India. *Indian J Cancer* 2012 Jan;49(1):176.
12. Chamseddine AN, Loulergue P, Mir O. HIV-Associated Cancers and Related Diseases. *N Eng J Med* 2018 May 31;378(22):2144.
13. Sinha S, Agarwal A, Gupta K, Mandal D, Jain M, Detels R, Nandy K, DeVos MA, Sharma SK, Manoharan N, Julka PK. Prevalence of HIV in patients with malignancy and of malignancy in HIV patients in a tertiary care center from North India. *Curr HIV Res* 2018 Jul 1;16(4):315-320.
14. Mocroft A, Ledergerber B, Katlama C, Kirk O, Reiss PD, Monforte AD, Knysz B, Dietrich M, Phillips AN, Lundgren JD, EuroSIDA Study Group. Decline in the AIDS and death rates in the EuroSIDA study: an observational study. *Lancet* 2003 Jul 5;362(9377):22-9.
15. Clifford GM, Franceschi S. Cancer risk in HIV-infected persons: influence of CD4+ count. *Future Oncol* 2009 Jun;5(5):669-78.
16. Clifford GM, Polesel J, Rickenbach M, Dal Maso L, Keiser O, Kofler A, Rapiti E, Levi F, Jundt G, Fisch T, Bordoni A. Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy. *J Natl Cancer Inst* 2005 Mar 16;97(6):425-32.
17. Akarolo-Anthony SN, Dal Maso L, Igbinoba F, Mbulaiteye SM, Adebamowo CA. Cancer burden among HIV-positive persons in Nigeria: preliminary findings from the Nigerian AIDS-cancer match study. *Infect Agent Cancer* 2014 Dec;9(1):1-7.
18. Phatak UA, Joshi R, Badakh DK, Gosavi VS, Phatak JU, Jagdale RV. AIDS-associated cancers: an emerging challenge. *J Assoc Physicians India* 2010 Mar 1;58:159-62.
19. Palefsky J. Human papillomavirus-related disease in people with HIV. *Curr Opin HIV AIDS* 2009 Jan;4(1):52.
20. Stier E. Human papillomavirus related diseases in HIV-infected individuals. *Curr Opin Oncol* 2008 Sep;20(5):541.
21. Sigel K, Dubrow R, Silverberg M, Crothers K, Braithwaite S, Justice A. Cancer screening in patients infected with HIV. *Curr HIV/AIDS Rep* 2011 Sep 1;8(3):142-52.
22. Bohlius J, Foster C, Naidu G, Sengayi M, Turkova A. Cancer in adolescents and young adults living with HIV. *Curr Opin HIV AIDS* 2018 May;13(3):196.
23. Dhokotera TG, Bohlius J, Egger M, Spoerri A, Ncayiyana J, Naidu G, Olago V, Zwahlen M, Singh E, Muchengeti M. Cancer in HIV-positive and HIV-negative adolescents and young adults in South Africa: a cross-sectional study. *medRxiv* 2020 Jan 1.

24. Beachler DC, D'Souza G. Oral HPV infection and head and neck cancers in HIV-infected individuals. *Curr Opin Oncol* 2013 Sep;25(5):503.
25. Traore B, Bah TS, Traore FA, Sow MS, Diane S, Keita M et al. The prevalence of HIV in cancer patients at the surgical oncology unit of Donka University Hospital of Conakry (Guinea). *J Cancer Epidemiol* 2015 Dec 3;2015.
26. Sankaranarayanan R, Budukh AM, Rajkumar R. Effective screening programmes for cervical cancer in low-and middle-income developing countries. *Bull World Health Organ* 2001;79:954-62.